CHAPTER 3

Principles of oncologic pharmacotherapy

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The effective use of cancer chemotherapy requires a thorough understanding of the principles of neoplastic cell growth kinetics, basic pharmacologic mechanisms of drug action, pharmacokinetic and pharmacodynamic variability, and mechanisms of drug resistance. Recent scientific advances in the field of molecular oncology have led to the identification of large numbers of potential targets for novel anticancer therapies. This has resulted in a tremendous expansion of the drug development pipeline, and in the present era, the diversity of clinically useful novel anticancer therapeutic agents is growing at an unprecedented rate. However, the great enthusiasm that surrounds these new agents must be tempered by the challenges they present in optimizing their clinical use and in rationally integrating them with existing anticancer therapies. This discussion focuses on the basic principles underlying the development of modern combination chemotherapy, and it is followed by a description of the major classes of chemotherapeutic drugs and their mechanisms of action.

The cell cycle and tumor growth kinetics

The growth pattern of individual neoplastic cells may greatly affect the overall biological behavior of human tumors and their responses to specific types of cancer therapy. Tumor cells can be subdivided into three general populations: (1) cells that are not dividing and are terminally differentiated; (2) cells that continue to proliferate; and (3) nondividing cells that are currently quiescent but may be recruited into the cell cycle. The kinetic behavior of dividing cells is best described by the concept of the cell cycle.

The cell cycle is composed of four distinct phases during which the cell prepares for and undergoes mitosis. The G_1 phase consists of cells that have recently completed division and are committed to continued proliferation. After a variable period of time, these cells begin to synthesize DNA, marking the beginning of the S phase. After DNA synthesis is complete, the end of the S phase is followed by the premitotic rest interval called the G_2 phase. Finally, chromosome condensation occurs and the cells divide during the mitotic M phase. Resting diploid cells that are not actively dividing are described as being in the G_0 phase. The transition between cell cycle phases is strictly regulated by specific signaling proteins; however, these cell cycle checkpoints may become aberrant in some tumor types.

Some anticancer agents induce their cytotoxic effects during specific phases of the cell cycle. Antimetabolites, such as fluorouracil and methotrexate, are more active against S-phase cells, whereas the vinca alkaloids, epipodophyllotoxins, and taxanes are relatively more M-phase specific. These kinetic properties may have clinically important consequences for cancer chemotherapy. For example, cell-cycle–nonspecific agents, such as the alkylating agents and platinum derivatives, generally have linear dose-response curves (ie, increasing the dose increases cytotoxicity). In contrast, cell-cycle–specific agents will often plateau in their concentration-dependent effects because only a subset of proliferating cells remain fully sensitive to drug-induced cytotoxicity. These cell-cycle–specific agents tend to be schedule dependent, because the only way to increase the total cell kill is by extending the duration of exposure, not by increasing the dose.

In early laboratory studies, Skipper found that murine leukemia cells grow in a logarithmic or exponential pattern because virtually all tumor cells are actively dividing in the cell cycle. When the logarithmic tumor growth reaches a critical level, the host animals die. However, when animals are treated with cancer chemotherapy, the reduction in viable tumor cells is not a fixed absolute number; instead, drug-induced cytoreduction follows first-order kinetics in which a fixed fraction of cells are killed. This can be quantified in terms of log cell kill; ie, the reduction in viable cells by 90% is a 1-log kill and a 99% reduction is a 2-log kill. Consequently, cancer chemotherapy is most effective and cures most likely when the absolute number of tumor cells is low.

Most human tumors do not display pure logarithmic growth patterns because not all cells within the tumor are actively dividing. In clinical practice, solid tumors typically have low growth fractions, heterogeneous doubling times, and as they increase in size, tumors may outgrow their blood and nutrient supply, leading to slower growth rates. In real life, most tumors display a sigmoid-shaped Gompertzian growth pattern in which growth rates decline as tumors expand in size. The most rapid growth occurs at small tumor volumes, whereas larger tumors may harbor higher numbers of nonproliferating cells, potentially

TABLE 1: Principles for selecting agents for use in combination chemotherapy regimens

Drugs known to be active as single agents should be selected for use in combinations; preferentially drugs that induce complete remission should be included.
Drugs with different mechanisms of action and with additive or synergistic cytotoxic effects on the tumor should be combined.
Drugs with different dose-limiting toxicities should be combined so that full or nearly full therapeutic doses can be utilized.
Drugs should be used at their optimal dose and schedule.
Drugs should be given at consistent intervals, and the treatment-free period should be as short as possible to allow for recovery for the most sensitive normal tissues.
Drugs with different patterns of resistance should be used to minimize cross-resistance.

making them less sensitive to agents that selectively target dividing cells. This understanding of tumor growth kinetics has been used to support the development of novel clinical strategies for optimizing cancer chemotherapy. This includes the use of adjuvant chemotherapy to treat small volumes of tumor cells during times of high growth rates and the sequential administration of non–cross-resistant drug combinations.

Principles of combination chemotherapy

Based upon cell kinetic and pharmacologic principles, a set of guidelines for designing modern combination chemotherapy regimens has been derived. Multiagent therapy has three important theoretical advantages over single-agent therapy. First, it can maximize cell kill while minimizing host toxicities by using agents with nonoverlapping dose-limiting toxicities. Second, it may increase the range of drug activity against tumor cells with endogenous resistance to specific types of therapy. Finally, it may also prevent or slow the development of newly resistant tumor cells. Specific principles for selecting agents for use in combination chemotherapy regimens are listed in Table 1.

DEFINITION OF RESPONSE

In clinical studies, formal response criteria have been developed and have gained wide acceptance. The National Cancer Institute (NCI) recently proposed and implemented newer standard response criteria called Response Evaluation Criteria in Solid Tumors (RECIST). In contrast, the World Health Organization (WHO) has a different standard for assessing response. Major differences are listed in Table 2.

TABLE 2: Comparison of RECIST and WHO guidelines

Characteristic	RECIST	WHO
Objective response (OR) (LD is the longest diameter)	**Target lesions** (change in sum of LDs, maximum 5 per organ up to 10 total [more than one organ])	**Measurable disease** (change in the sum of the products of LDs and greatest perpendicular diameters, no maximum number of lesions specified)
Complete response (CR)	Disappearance of all target lesions, confirmed at ≥ 4 weeks	Disappearance of all known disease, confirmed at ≥ 4 weeks
Partial response (PR)	≥ 30% decrease from baseline, confirmed at ≥ 4 weeks	≥ 50% decrease from baseline, confirmed at ≥ 4 weeks
Progressive disease (PD)	≥ 20% increase over smallest sum observed or appearance of new lesions	≥ 25% increase in one or more lesions or appearance of new lesions
Stable disease (SD)	Neither PR nor PD criteria met	Neither PR nor PD criteria met (no change)

DRUG RESISTANCE

Drug resistance to chemotherapy may arise from a variety of different mechanisms, including anatomic, pharmacologic, and genetic processes. Some of the common factors that may broadly affect tumor cell sensitivity to different classes of agents include the failure of drugs to penetrate into specific sanctuary sites, such as the brain and testes, or the development of mutations in the target proteins rendering them less sensitive to specific molecular inhibitors. Another factor may be decreased drug accumulation resulting from the increased expression of drug efflux pumps in the cell membrane, such as *p*-glycoprotein, which is encoded for by the multidrug resistance (MDR-1) gene. This 170-kDa glycoprotein normally removes toxins or xenobiotic metabolites from cells via an energy-dependent process. High levels of MDR-1 expression in tumor cells correlate with resistance to a wide range of cytotoxic agents. Other drug efflux pumps that have been implicated in the development of broad resistance to cancer chemotherapy include the MDR-associated protein (MRP) and breast cancer resistance protein (BCRP).

Pharmacokinetic and pharmacodynamic variability

VARIABILITY IN CLEARANCE

The rational clinical use of cancer chemotherapy requires a thorough understanding of the variability in human response to drug therapy. One of the major goals of the field of clinical pharmacology is to precisely define the processes responsible for this variability in drug action. Pharmacokinetic variability can arise from interindividual differences in drug adsorption, distribution, metabolism, and excretion. All of these processes result in differences in drug delivery to its ultimate site of action. In contrast, pharmacodynamic variability arises from inherent differences in the sensitivity of target tissues to drug effects. Both kinetic and dynamic factors can complicate the treatment of individual cancer patients and must be addressed by the practicing oncologist on a daily basis. Although a formal review of drug pharmacokinetics and pharmacodynamics is not possible here, a brief discussion of the most clinically relevant points is warranted.

The most clinically useful parameter in drug therapy is clearance, because clearance reflects all the processes in the body that contribute to drug elimination. In oncology, the importance of clearance is enhanced because clearance is the only parameter that relates dose to the measured area under the concentration vs time curve (AUC), which is a useful measure of systemic drug exposure. Mathematically, clearance is defined by CL = dose/AUC. Clearance is not a rate of drug elimination; instead it is defined as a volume of drug cleared per unit of time.

Overcoming interindividual variation in clearance is a fundamental goal of pharmacokinetic analyses. Because they tend to be highly toxic with low efficacy, anticancer drugs may have the narrowest therapeutic index of any class

of agents used in clinical medicine. Thus, the ability to administer an individualized dose of drug to achieve a uniform target AUC and a uniform clinical result is often a high priority for cancer therapeutics. Because CL defines the relationship between dose and AUC, estimating clearance prior to anticancer drug administration is extremely important. A common attempt to individualize cancer chemotherapy is to dose a drug based upon the body surface area (BSA) expressed in mg/m^2 to achieve a uniform AUC in patients with different body sizes. Inherent in this approach is the fundamental assumption that clearance is strongly correlated with BSA. However, when studied formally, the relationship between clearance and BSA is often weak and does not consistently justify the routine use of this dosing approach. Nonetheless, although the application of BSA-based dosing has been widely criticized, it still remains a common practice.

Recognizing clinical situations in which drug clearance is commonly altered, such as in patients with hepatic or renal dysfunction, is important for agents that are eliminated by these routes. For example, carboplatin (Paraplatin) is extensively cleared by glomerular filtration, and its systemic AUC in plasma ultrafiltrates is strongly correlated with pharmacodynamic effects, such as thrombocytopenia. Thus, dosing strategies that estimate the glomerular filtration rate (GFR) to achieve a targeted AUC and thereby minimize excessive toxicity in individual patients have gained wide clinical acceptance. Likewise, for hepatically metabolized drugs, doses must be adjusted in patients with liver dysfunction. However, accurately assessing hepatic drug-metabolizing capacity is more difficult than estimating the GFR. Nonetheless, guidelines for dose-adjusting agents metabolized in the liver, such as doxorubicin, have been established.

PHARMACOGENOMIC VARIABILITY

Variability in drug action may also be caused by genetic factors. The new field of pharmacogenomics attempts to define the impact of genetic differences on drug kinetics and dynamics. McLeod and Evans have defined pharmacogenomics as the field of study of "the inherited nature of interindividual differences in drug disposition and effects." Clinically relevant genetic variations have been characterized in specific drug-metabolizing enzyme, such as the cytochrome P-450 isoforms CYP2D6 and CYP2C9.

In the field of medical oncology, well-defined examples of clinically relevant pharmacogenetic differences are relatively few; however, this is an important area of ongoing research. Perhaps the best characterized example in clinical oncology is the inherited deficiency of the thiopurine methyltransferase (TPMT) enzyme that results in severe intolerance to thiopurine therapy. Another example is the inherited variation in dihydropyrimidine dehydrogenase (DPD) activity, the rate-limiting catabolic enzyme responsible for fluorouracil clearance. Genetic alterations associated with DPD deficiency have been identified in rare patients experiencing severe and fatal toxicity after treatment with standard doses of fluorouracil. Finally, interindividual variation in irinotecan (Camptosar)-induced toxicities may be partially explained by genetic poly-

morphisms in the gene encoding the UDP-glucuronosyltransferase (UGT) 1A1 enzyme that is involved in the clearance of the active metabolite SN-38.

Pharmacodynamic polymorphisms that directly affect target tissue sensitivity to drug effects are also clinically important. For example, polymorphisms in the promoter region of the thymidylate synthase gene have been correlated with tumor response to fluorouracil-based chemotherapy that targets this enzyme. In the near future, our understanding of how genetics affects a drug's pharmacokinetics may ultimately allow for the optimization of specific treatment regimens for individual patients. Likewise, our understanding of how genetics affects pharmacodynamic variation may be enhanced by powerful new technologies that can characterize the expression of literally thousands of genes within the tumor itself. The molecular profiling of tumor cells by DNA microarray techniques and other advances in biotechnology offer tremendous hope for improving our ability to treat cancer in the near future.

Molecularly targeted therapies

At the beginning of the 21st century, important and meaningful advances in anticancer therapeutics are being discovered at an unparalleled rate. Much of this progress is driven by the explosion of knowledge in the field of molecular oncology. The sequencing of the entire human genome has dramatically increased the number of promising molecular targets for new and novel anticancer treatment strategies. These advances hold great promise for developing a new generation of agents with high specificity for tumor cells (see discussion later in this chapter).

Chemotherapeutic agents classified by mechanism of action

Alkylating agents

The alkylating agents impair cell function by forming covalent bonds with the amino, carboxyl, sulfhydryl, and phosphate groups in biologically important molecules. The most important sites of alkylation are DNA, RNA, and proteins. The electron-rich nitrogen at the 7 position of guanine in DNA is particularly susceptible to alkylation.

Alkylating agents depend on cell proliferation for activity but are not cell-cycle-phase–specific. A fixed percentage of cells are killed at a given dose. Tumor resistance probably occurs through efficient glutathione conjugation or by enhanced DNA repair mechanisms. Alkylating agents are classified according to their chemical structures and mechanisms of covalent bonding; this drug class includes the nitrogen mustards, nitrosoureas, and platinum complexes, among other agents (see Table 3).

Nitrogen mustards The nitrogen mustards, which include such drugs as mechlorethamine (Mustargen), cyclophosphamide (Cytoxan, Neosar), ifosfamide (Ifex), and chlorambucil (Leukeran), are powerful local vesicants; as

TABLE 3: Alkylating agents and their uses, dosages, and toxicities

Drug and its uses[a]	Dosages	Toxicities[b]
Nitrogen mustards		
Chlorambucil *CLL, HD, NHL,* ovarian cancer, choriocarcinoma, lymphosarcoma	0.1-0.2 mg/kg PO daily for 3-6 wk as required (usually 4-10 mg/d) or intermittent 0.4 mg/kg every 3-4 wk; increase by 0.1 mg/kg until control of disease or toxicity	*Bone marrow depression,* gonadal dysfunction, leukemia, hyperuricemia, pulmonary fibrosis
Cyclophosphamide *AML, ALL, CLL, HD, and NHL, multiple myeloma, mycosis fungoides, neuroblastoma, ovarian and breast cancers, retinoblastoma,* lung, testicular, and bladder cancers, sarcoma	40-50 mg/kg IV in divided doses over 2-5 d to start, followed by 10-15 mg/kg IV every 7-10 d; or 3-5 mg/kg IV twice weekly; or 1-5 mg/kg/d PO	*Bone marrow depression,* hemorrhagic cystitis, immunosuppression, alopecia, stomatitis, SIADH
Estramustine *Prostate, renal cell carcinoma*	14 mg/kg/d PO in 3-4 equally divided doses; 300 mg/d IV for 3-4 wk, followed by 300-450 mg/wk IV over 3-8 wk	*Bone marrow depression,* ischemic heart disease, thromboembolism, thrombophlebitis gynecomastia, nausea and vomiting, hepatotoxicity
Ifosfamide *Germ-cell testicular cancer,* sarcoma, NHL, lung cancer	1.2 g/m^2/d via slow IV infusion for 5 consecutive days; repeat every 3 wk; give with mesna	*Bone marrow depression, hemorrhagic cystitis,* confusion, somnolence
Mechlorethamine *HD, NHL, CML, CLL, mycosis fungoides, bronchogenic carcinoma,* lymphosarcoma, polycythemia vera, malignant effusions (intracavitary)	0.4 mg/kg ideal body weight given as single dose or in divided doses of 0.1-0.2 mg/kg/d	*Bone marrow depression, nausea and vomiting,* local phlebitis, severe skin necrosis if extravasated, gonadal dysfunction
Melphalan *Multiple myeloma, breast and ovarian cancers, sarcoma,* testicular and lung cancers	Continuous therapy: 6 mg PO daily for 2-3 wk, no therapy for 2-4 wk, then maintenance with 2-4 mg PO daily Pulse: 10 mg/m^2 PO daily for 4 d every 4-6 wk	*Bone marrow depression,* anorexia, nausea and vomiting, gonadal testicular dysfunction, leukemia

[a] FDA-approved uses in italics; neoplasms are carcinomas unless otherwise indicated

[b] Dose-limiting effects in italics

continued on following page

TABLE 3: Alkylating agents and their uses, dosages, and toxicities *(continued)*

Drug and its uses[a]	Dosages	Toxicities[b]
Aziridine		
Thiotepa *Ovarian, breast, and superficial bladder cancers,* HD, CML, CLL, bronchogenic carcinoma, malignant effusions (intracavitary), BMT for refractory leukemia, lymphomas	IV: 0.3-0.4 mg/kg by rapid IV infusion Intravesical: 60 mg/60 mL sterile water instilled and retained in bladder for 2 h; repeat weekly for 4 wk Intracavitary: 0.6-0.8 mg/kg	*Bone marrow depression,* nausea and vomiting, mucositis, skin rashes
Alkyl sulfonate		
Busulfan *CML,* BMT for refractory leukemia, lymphomas	2-8 mg PO daily for remission induction; adjust dosage to WBC count; 1-3 mg PO daily for maintenance; withhold induction if WBC count < 15,000/μL; resume therapy when WBC count > 50,000/μL	*Bone marrow depression, pulmonary fibrosis,* aplastic anemia, amenorrhea, gynecomastia, skin hyperpigmentation
Nitrosoureas		
Carmustine *Brain tumor, multiple myeloma, HD, NHL,* melanoma, BMT for refractory solid tumors and lymphomas	150-200 mg/m^2 IV every 6-8 wk	*Delayed bone marrow depression,* nausea and vomiting, reversible hepatotoxicity, local phlebitis, pulmonary and renal damage (high dose)
Gliadel wafers *Glioblastoma multiforme*	Up to 8 wafers placed in the brain cavity created by tumor removal	Fever, pain, and abnormal healing
Lomustine *Brain tumors, HD,* GI carcinomas, NSCLC	130 mg/m^2 PO every 6 wk; adjust dose in combination chemotherapy	*Delayed bone marrow depression,* nausea and vomiting, reversible hepatotoxicity, pulmonary and renal damage, neurologic reactions, leukemia
Streptozocin *Pancreatic islet-cell,* carcinoid, colon, hepatoma, NSCLC, HD	Daily: 500 mg/m^2 IV for 5 d every 6 wk until maximum benefit or toxicity Weekly: 1,000 mg/m^2 IV weekly for first 2 wk, then escalate dose to response or toxicity, not to exceed a single dose of 1,500 mg/m^2	*Renal damage,* nausea and vomiting, diarrhea, altered glucose metabolism, liver dysfunction

ALL = acute lymphoblastic leukemia; AML = acute myelogenous leukemia; AUC = area under the curve; BMT = bone marrow transplantation; CLL = chronic lymphocytic leukemia; CML = chronic myelogenous leukemia; CMML = chronic myelomacrocytic leukemia; 5-FU = fluorouracil; GFR = glomerular filtration rate; HD = Hodgkin's disease; MDS = myelodysplastic syndromes; MOPP = mechlorethamine, Oncovin, procarbazine, and prednisone; NHL = non-Hodgkin's lymphoma; NSCLC = non–small-cell lung cancer; SCLC = small-cell lung cancer; SIADH = syndrome of inappropriate antidiuretic hormone secretion; WBC = white blood cell

Drug and its uses[a]	Dosages	Toxicities[b]
Platinum complexes		
Carboplatin *Ovarian cancer,* endometrial, head and neck, lung, testicular, and breast cancers, relapsed acute leukemia, NHL	Single agent: 360 mg/m^2 IV every 4 wk Combination: 300 mg/m^2 IV every 4 wk Calvert formula: Total dose (mg) = Target AUC × (GFR + 25)	*Bone marrow depression,* nausea and vomiting, peripheral neuropathy, ototoxicity
Cisplatin *Testicular, ovarian, bladder,* uterine, cervical, and lung cancers, squamous cell cancer of the head and neck, sarcoma, NHL	50 mg/m^2 IV or more every 3 wk; or 20 mg/m^2 IV daily for 4-5 d every 3-4 wk; give vigorous hydration before and after chemotherapy	*Renal damage,* nausea and vomiting, electrolyte disturbance, peripheral neuropathy, bone marrow depression, ototoxicity, radiosensitizer
Oxaliplatin *Colorectal,* ovarian cancer	85 mg/m^2 oxaliplatin and 200 mg/m^2 leucovorin (lv) IV infusion over 120 min on d 1 followed by 400 mg/m^2 5-FU IV bolus, then 600 mg/m^2 5-FU by IV infusion over 22 h. On d 2, 200 mg/m^2 lv over 120 min IV, followed by 400 mg/m^2 5-FU IV bolus, 600 mg/m^2 5-FU IV infusion over 22 h. Repeat every 2 wk.	*Bone marrow depression, diarrhea,* nausea and vomiting, neuropathies exacerbated by cold exposure, pharyngolaryngeal dysesthesia
Nonclassic alkylators		
Altretamine *Ovarian,* lung, breast, and cervical cancers, NHL	4-12 mg/kg/d or 260 mg/m^2, PO divided in 3-4 doses for 14-21 d of a 28-d regimen	*Nausea and vomiting*, bone marrow depression, paresthesias, CNS toxicity
Dacarbazine *Malignant melanoma, HD,* soft-tissue sarcomas, neuroblastoma	Melanoma: 2.0-4.5 mg/kg/d IV for 10 d every 4 wk; or 250 mg/m^2/d IV for 5 d every 3 wk HD: 375 mg/m^2 IV on d 1, repeated every 15 d (single agent); 150 mg/m^2/d IV for 5 d every 4 wk (combination therapy)	*Bone marrow depression,* nausea and vomiting, flulike syndrome, transient hepatotoxicity, local irritation, facial flushing, alopecia
Procarbazine *HD,* NHL, brain tumors, lung cancer	Single agent: 4-6 mg/kg/d PO until maximum response HD (MOPP): 100 mg/m^2/d PO for 14 d	*Bone marrow depression,* nausea and vomiting, lethargy, depression, paresthesias, headache, flulike symptoms
Temozolomide *Anaplastic astrocytoma (relapsed)*, renal cell cancer, melanoma	150 mg/m^2/d PO for 5 d every 28 d	*Bone marrow depression*, nausea and vomiting

TABLE 4: Antimetabolites and their uses, dosages, and toxicities

Drug and its uses[a]	Dosages	Toxicities[b]
Folate analog		
Methotrexate *Breast, head and neck, GI, and lung cancers, ALL, CNS leukemia (intrathecal), gestational trophoblastic tumors, NHL (advanced stage),* Burkitt's lymphoma, osteosarcoma, mycosis fungoides	Numerous dosing schedules with combination therapy: Low dose: 2.5-5.0 mg PO daily; or 5-25 mg/m^2 PO, IM, IV twice weekly; or 50 mg/m^2 IV every 2-3 wk High dose: 1-12 g/m^2 IV with leucovorin rescue every 1-3 wk Intrathecal: 5-10 mg/m^2 (up to 15 mg) every 3-7d	*Mucositis, GI ulceration (may produce hemorrhage or perforation), bone marrow depression, pulmonary fibrosis (previously irradiated area),* nerve root irritation and convulsion (intrathecal), liver cirrhosis and osteoporosis (chronic therapy), renal damage (high dose), diarrhea, skin erythema
Pemetrexed *Mesothelioma, NSCLC*	500 mg/m^2 IV over 10 min every 21 d	*Bone marrow depression.* stomatitis/pharyngitis, rash/skin desquamation
Purine analogs		
Fludarabine *CLL,* AML, NHL (low-grade)	25 mg/m^2/d IV over 30 min for 5 d; repeat every 28 d	*Bone marrow depression,* nausea and vomiting, fever, malaise, pulmonary infiltrates, tumor lysis syndrome, CNS effects (high dose)
Mercaptopurine *ALL, CML, AML*	1.5-2.5 mg/kg/d PO (100-200 mg in average adult) until response or toxic effects are seen; may increase dose to 5 mg/kg/d; adjust for maintenance dose; reduce dose by 50%-75% if given with allopurinol or if renal or hepatic insufficiency ensues	*Bone marrow depression,* nausea and vomiting, anorexia, diarrhea, cholestasis
Thioguanine *AML,* ALL, CML, advanced colorectal cancer, multiple myeloma	2 mg/kg/d PO until response or toxic effects are seen; may cautiously increase to 3 mg/kg/d	*Bone marrow depression,* liver damage, stomatitis
Adenosine analogs		
Cladribine *Hairy-cell leukemia,* NHL, mycosis fungoides, AML, CML, CLL	0.09 mg/kg/d (4 mg/m^2/d) by continuous IV infusion for 7 consecutive days	*Bone marrow depression,* febrile episodes, rash, infections, septicemia
Pentostatin *Hairy-cell leukemia,* ALL, CLL, lymphoblastic lymphoma, mycosis fungoides	4 mg/m^2 IV over 30 min every other week or for 3 consecutive weeks; give vigorous hydration before and after chemotherapy	*Nephrotoxicity, CNS depression,* bone marrow depression, nausea and vomiting, conjunctivitis

[a] FDA-approved uses in italics; neoplasms are carcinomas unless otherwise indicated

[b] Dose-limiting effects in italics

Drug and its uses[a]	Dosages	Toxicities[b]
Pyrimidine analogs		
Capecitabine *Breast cancer (relapsed), colorectal cancer, and other GI malignancies*	1,250 mg/m^2 bid PO with food (2 weeks on drug, 1 week of rest)	*Diarrhea*, stomatitis, nausea and vomiting, fatigue, hand-foot syndrome, bone marrow depression (minimal)
Cytarabine *AML,* ALL, CML, NHL, CNS leukemia (intrathecal)	AML induction: 100 mg/m^2/d by continuous IV infusion on days 1-7; or 100 mg/m^2 IV every 12 h on days 1-7 Relapsed ALL: 3 g/m^2 IV over 1-3 h every 12 h for 4 doses	*Bone marrow depression,* nausea and vomiting, diarrhea, arachnoiditis (intrathecal), stomatitis, hepatic dysfunction, fever, conjunctivitis, confusion, somnolence, cerebellar toxicity
DepoCyt (liposomal cytarabine) *CNS leukemia/lymphoma*	Intrathecal: DepoCyt, 50 mg over 1-5 min every 14 d, with dexamethasone, 4 mg PO bid × 5 d	
Floxuridine *GI adenocarcinomas metastatic to liver,* including oral, pancreatic, biliary, colon, and hepatic cancers, and metastatic breast cancer	0.1-0.6 mg/kg/d over several days via continuous arterial infusion supplying well-defined tumor; treatments given over 1-6 wk	*Stomatitis and GI ulcers, bone marrow depression,* abdominal pain, nausea and vomiting, diarrhea, liver dysfunction (transient)
Fluorouracil *Colon, rectal, stomach, pancreatic, breast,* head and neck, renal cell, prostate, and ovarian cancers, squamous cell carcinomas of esophagus, basal and squamous cell carcinoma of skin (topical), hepatic cancer (intra-arterial)	Numerous dosing schedules with combination therapy: Loading dose: 300-500 mg/m^2; or 12 mg/kg IV daily for 3-5 d, followed by weekly maintenance Maintenance: 10-15 mg/kg IV weekly, as toxicity permits Infusion: 20-25 mg/kg by continuous IV infusion over 24 h daily for 4-5 d, every 4 wk	*Stomatitis and GI ulcers (infusion) bone marrow depression (bolus), diarrhea,* nausea and vomiting, esophagitis, angina, cerebellar ataxia, radiosensitizer
Gemcitabine *Pancreatic, lung, breast,* ovarian, and bladder cancers	1,000 mg/m^2 IV over 30 min, once weekly for up to 7 wk (or until toxicity necessitates reducing or withholding a dose), followed by 1 wk of rest Subsequent cycles: Infusions once weekly for 3 consecutive weeks out of every 4 wk	*Bone marrow depression,* transient fever, flulike syndrome, skin rash, mild nausea and vomiting
Substituted urea		
Hydroxyurea *CML, acute leukemia (emergent treatment), head and neck cancer, ovarian cancer, melanoma,* essential thrombocytosis, polycythemia vera	Intermittent: 80 mg/kg PO every third day Continuous: 20-30 mg/kg PO daily	*Bone marrow depression,* mild nausea and vomiting, skin rashes, radiosensitizer

(See Table 3 for abbreviations)

TABLE 5: Natural products and their uses, dosages, and toxicities

Drug and its uses[a]	Dosages	Toxicities[b]
Antitumor antibiotics		
Bleomycin *Testicular cancer, HD, reticulum cell sarcoma, lymphosarcoma, squamous cell cancer of the head and neck, skin, cervix, vulva, and penis*	10-20 U/m^2 given IV, IM, or SC weekly or twice weekly; maximum total dose, 400 U; a 2-U test dose should be given because of a possible anaphylactoid reaction	*Pneumonitis and pulmonary fibrosis,* fever and allergic reactions, anaphylaxis, hyperpigmentation, Raynaud's phenomenon, alopecia
Dactinomycin *Testicular cancer, gestational trophoblastic tumors, Wilms' tumor, rhabdomyosarcoma, Ewing's sarcoma*	0.010-0.015 mg/kg IV daily for 5 d every 3 wk (usual adult dose, 0.5 mg) or 2 mg/m^2 IV as a single dose every 3-4 wk	*Stomatitis, bone marrow depression,* anorexia, nausea and vomiting, diarrhea, alopecia, skin changes, anaphylactoid reaction
Daunorubicin *AML, ALL*	Remission induction: 30-45 mg/m^2/d IV for 3 d in combination therapy; total cumulative dose, 550 mg/m^2	*Bone marrow depression,* cardiotoxicity, alopecia, nausea and vomiting, diarrhea, stomatitis, fever, dermatitis at previously irradiated sites, red urine, anaphylactoid reaction
DaunoXome (liposomal daunorubicin) *Kaposi's sarcoma*	Liposomal preparation: 40 mg/m^2 IV every 2 wk	
Doxorubicin *ALL, AML, breast, ovarian,* bladder cancers, HD, NHL, SCLC, gastric cancer, sarcoma, Wilms' tumor, neuroblastoma, thyroid cancer	60-90 mg/m^2 single IV injection every 21 d, 20-30 mg/m^2/d IV for 3 d every 3-4 wk, or 20 mg/m^2 IV weekly; total cumulative dose of 550 mg/m^2; reduce dose for liver dysfunction	*Bone marrow depression, cardiotoxicity, stomatitis (continuous infusion),* alopecia, nausea and vomiting, diarrhea, fever, dermatitis at previously irradiated sites, red urine, anaphylactoid reaction
Doxil (liposomal doxorubicin) *Ovarian cancer (refractory to paclitaxel- and platinum-based regimens), Kaposi's sarcoma*	50 mg/m^2 IV every 4 wk 20 mg/m^2 IV every 3 wk	*Bone marrow depression,* hand-foot syndrome
Epirubicin *Breast cancer*	100 mg/m^2 IV on day 1 or 60 mg/m^2 IV on days 1 and 8 in combination therapy	*Bone marrow depression, cardiotoxicity, stomatitis,* alopecia
Idarubicin *AML,* CML (blast phase), ALL	12 mg/m^2/d IV for 3 d every 3 wk in combination therapy	*Bone marrow depression,* nausea and vomiting, stomatitis, alopecia, cardiotoxicity

[a] FDA-approved uses in italics; neoplasms are carcinomas unless otherwise indicated

[b] Dose-limiting effects in italics

Drug and its uses[a]	Dosages	Toxicities[b]
Mitoxantrone *AML, prostate,* ALL, CML, breast and ovarian cancers	Remission induction: 12 mg/m^2/d IV for 3 d, in combination with Ara-C	*Bone marrow depression*, cardiotoxicity, alopecia, stomatitis, nausea and vomiting, blue urine and sclera
Mitomycin *Gastric, colorectal, pancreatic adenocarcinomas,* NSCLC, breast, uterine, cervical, and head and neck cancers	20 mg/m^2 IV every 6-8 wk as a single agent or 5-10 mg/m^2 IV every 6 wk in combination therapy	*Bone marrow depression (cumulative),* nausea and vomiting, anorexia, alopecia, stomatitis, fever, pulmonary fibrosis
Valrubicin *Bladder*	800 mg IV once a week for 6 wk	*Local bladder symptoms*
Epipodophyllotoxins		
Etoposide *Testicular cancer (refractory), SCLC,* HD, NHL, AML, gestational trophoblastic tumors	Testicular: 50-100 mg/m^2/d IV for 5 d or 100 mg/m^2/d IV on days 1, 3, and 5 Lung: 35-50 mg/m^2/d IV for 5 d or 100 mg/m^2/d PO for 5 d For both indications, given with combination therapy and repeated every 3-4 wk	*Bone marrow depression,* nausea and vomiting, diarrhea, fever, hypotension with rapid infusion, alopecia, rash
Teniposide *Relapsed ALL in children,* SCLC	ALL: 100 mg/m^2 once or twice weekly or 20-60 mg/m^2/d for 5 d in combination with Ara-C Lung: 80-90 mg/m^2/d for 5 d as a single agent	*Bone marrow depression,* nausea and vomiting, alopecia, hypotension with rapid infusion, increased liver enzymes
Microtubule agents		
Docetaxel *Breast (relapsed), NSCL prostate,* ovarian, pancreatic, head and neck, esophagus, stomach, cervical, Kaposi's sarcoma, uterine, and bladder cancers	60-100 mg/m^2 IV over 1 h every 21 d; or up to 42 mg/m^2 IV every week	*Bone marrow depression,* fluid retention, hypersensitivity reaction, paresthesias, rash, alopecia, myalgias
Paclitaxel *Ovarian cancer, (relapsed), NSCLC (in combination with cisplatin), Kaposi's sarcoma, breast cancer (relapsed),* head and neck, gastric, colon, esophagus, uterine, prostate, bladder cancers and melanomas	135-175 mg/m^2 by IV infusion (ranging from 3-96 h) every 3 wk; or 80 mg/m^2 IV every week	*Bone marrow depression* peripheral neuropathy, alopecia, mucositis, anaphylaxis, dyspnea, myalgias

continued on following page

TABLE 5: Natural products and their uses, dosages, and toxicities *(continued)*

Drug and its uses[a]	Dosages	Toxicities[b]
Vinblastine *HD, NHL, gestational trophoblastic tumors, testicular and breast cancers, mycosis fungoides, Kaposi's sarcoma, histiocytosis X,* bladder and renal cancers, NSCLC, CML (blast crisis)	4-12 mg/m^2 IV as a single agent every 1-2 wk; titrate dose to myelosuppression; adjust for hepatic insufficiency	*Bone marrow depression,* nausea and vomiting, ileus, alopecia, stomatitis, myalgias, vesication
Vincristine *ALL, HD, NHL, rhabdomyosarcoma, neuroblastoma, Wilms' tumor,* multiple myeloma, sarcomas, breast cancer	0.4-1.4 mg/m^2 IV weekly; maximum total dose, 2 mg/wk; reduce dose for hepatic insufficiency	*Peripheral neuropathy,* ileus, abdominal pain, SIADH, bone marrow depression (mild)
Vinorelbine *NSCLC,* breast, ovarian, head and neck cancers, HD	30 mg/m^2 IV over 10 min; repeat weekly	*Peripheral neuropathy, bone marrow depression,* nausea and vomiting, hepatic dysfunction
Camptothecin analogs		
Irinotecan *Colorectal cancer,* lung, ovarian, and cervical cancers	125 mg/m^2 IV over 90 min once weekly for 4 wk; then 2 wk rest; or 350 mg/m^2 every 21 d	*Bone marrow depression, diarrhea,* nausea and vomiting anorexia, weight loss
Topotecan *Ovarian cancer (relapsed), SCLC (relapsed),* MDS, CMML	1.5 mg/m^2 IV over 30 min for 5 consecutive days at 21-d intervals	*Bone marrow depression,* fever, flulike symptoms, nausea and vomiting
Enzyme		
Asparaginase *ALL,* CML, AML	6,000 IU/m^2 IM 3 times weekly for 9 doses or 100 IU/kg/d IV for 10 continuous days, starting on day 22 of treatment; usually given with vincristine and prednisone	*Allergic reactions (fever, chills skin rash, anaphylaxis),* nausea and vomiting, anorexia, liver dysfunction, CNS depression, coagulopathy, hyperglycemia

(See Table 3 for abbreviations)

such, they can cause problems ranging from local tissue necrosis, to pulmonary fibrosis, to hemorrhagic cystitis. The metabolites of these compounds are highly reactive in aqueous solution, in which an active alkylating moiety, the ethylene immonium ion, binds to DNA. The hematopoietic system is especially susceptible to these compounds.

Nitrosoureas The nitrosoureas are distinguished by their high lipid solubility and chemical instability. These agents rapidly and spontaneously decompose into two highly reactive intermediates: chloroethyl diazohydroxide and isocyanate. The lipophilic nature of the nitrosoureas enables free passage across membranes; therefore, they rapidly penetrate the blood-brain barrier, achieving effective CNS concentrations. As a consequence, these agents are used for a variety of brain tumors.

Platinum agents Cisplatin is an inorganic heavy metal complex that has activity typical of a cell-cycle-phase–nonspecific alkylating agent. The compound produces intrastrand and interstrand DNA cross-links and forms DNA adducts, thereby inhibiting the synthesis of DNA, RNA, and proteins. Carboplatin has the same active diamine platinum moiety as cisplatin, but it is bonded to an organic carboxylate group that allows increased water solubility and slower hydrolysis to the alkylating aqueous platinum complex, thus altering toxicity profiles. Oxaliplatin (Eloxatin) is distinguished from the other platinum compounds by a di-amino-cyclohexane ring bound to the platinum molecule, which interferes with resistance mechanisms to the drug.

Antimetabolites

Antimetabolites are structural analogs of the naturally occurring metabolites involved in DNA and RNA synthesis. As the constituents of these metabolic pathways have been elucidated, a large number of structurally similar drugs that alter the critical pathways of nucleotide synthesis have been developed.

Antimetabolites exert their cytotoxic activity either by competing with normal metabolites for the catalytic or regulatory site of a key enzyme or by substituting for a metabolite that is normally incorporated into DNA and RNA. Because of this mechanism of action, antimetabolites are most active when cells are in the S phase and have little effect on cells in the G_0 phase. Consequently, these drugs are most effective against tumors that have a high growth fraction.

Antimetabolites have a nonlinear dose-response curve, such that after a certain dose, no more cells are killed despite increasing doses (fluorouracil is an exception). The antimetabolites can be divided into folate analogs, purine analogs, adenosine analogs, pyrimidine analogs, and substituted ureas (see Table 4).

Natural products

A wide variety of compounds possessing antitumor activity have been isolated from natural substances, such as plants, fungi, and bacteria. Likewise, selected compounds have semisynthetic and synthetic designs based on the active chemical structure of the parent compounds, and they, too, have cytotoxic effects (see Table 5).

Antitumor antibiotics Bleomycin preferentially intercalates DNA at guanine-cytosine and guanine-thymine sequences, resulting in spontaneous oxidation and formation of free oxygen radicals that cause strand breakage.

Anthracyclines The anthracycline antibiotics are products of the fungus *Streptomyces percetus* var *caesius.* They are chemically similar, with a basic anthracycline structure containing a glycoside bound to an amino sugar, daunosamine. The anthracyclines have several modes of action. Most notable are intercalation between DNA base pairs and inhibition of DNA–topoisomerases I and II. Oxygen free radical formation from reduced doxorubicin intermediates is thought to be a mechanism associated with cardiotoxicity.

Epipodophyllotoxins Etoposide is a semisynthetic epipodophyllotoxin extracted from the root of *Podophyllum peltatum* (mandrake). It inhibits topoisomerase II activity by stabilizing the DNA–topoisomerase II complex; this process ultimately results in the inability to synthesize DNA, and the cell cycle is stopped in the G_1 phase.

Vinca alkaloids The vinca alkaloids are derived from the periwinkle plant *Vinca rosea.* Upon entering the cell, vinca alkaloids bind rapidly to the tubulin. The binding occurs in the S phase at a site different from that associated with paclitaxel and colchicine. Thus, polymerization of microtubules is blocked, resulting in impaired mitotic spindle formation in the M phase.

Taxanes Paclitaxel and docetaxel (Taxotere) are semisynthetic derivatives of extracted precursors from the needles of yew plants. These drugs have a novel 14-member ring, the taxane. Unlike the vinca alkaloids, which cause microtubular disassembly, the taxanes promote microtubular assembly and stability, therefore blocking the cell cycle in mitosis. Docetaxel is more potent than paclitaxel in enhancing microtubular assembly and also induces apoptosis.

Camptothecin analogs include irinotecan and topotecan (Hycamtin). These semisynthetic analogs of the alkaloid camptothecin, derived from the Chinese ornamental tree *Camptotheca acuminata*, inhibit topoisomerase I and interrupt the elongation phase of DNA replication.

Monoclonal antibodies

Although monoclonal antibodies (MAbs) have been used in cancer therapeutics since the late 1990s, the number of new agents in this class is growing exponentially (Table 6). Several unconjugated MAbs have established utility in medical oncology as highly targeted therapies. The earliest therapeutic MAb to show convincing utility in medical oncology was rituximab (Rituxan), approved in 1997 for the treatment of non-Hodgkin's lymphoma. This antibody targets the CD20 antigen found on B-cell lymphocytes and can be used clinically as a single agent or in association with combination chemotherapy. Another MAb, trastuzumab (Herceptin), has shown excellent activity in combination with chemotherapy in breast cancer patients whose tumor cells overexpress the HER2 protein. Finally, alemtuzumab (Campath) is a MAb that recognizes the CD52 antigen expressed on both B-cell and T-cell lymphocytes. This agent is useful in the treatment of chemotherapy-refractory B-

TABLE 6: Monoclonal antibodies and and their uses, dosages, and toxicities

Drug and its uses[a]	Dosages	Toxicities[b]
Rituximab *CD20-positive B-cell NHL*	375 mg/m^2 IV infusion (50-100 mg/h) once weekly	Infusion reactions, asthenia, headache, skin rash/pruritus, leukopenia/infection, nausea, tumor lysis syndrome
Trastuzumab *HER2-overexpressing breast cancer*	4 mg/kg IV over 90 min, loading dose, and 2 mg/kg IV over 30 min every 7 d, as maintenance	Cardiac failure, infusion reaction, diarrhea
Alemtuzumab *Chemotherapy-refractory B-cell CLL*	Rapid daily dose escalation, until tolerated, from 3 mg/d, and then 10 mg/d, to the recommended maintenance dose of 30 mg IV over 120 min, three times per wk on alternate days for up to 12 wk	*Pancytopenia*, infusion reaction, opportunistic infections, skin rash, nausea/vomiting
Cetuximab *EGFR-expressing colorectal cancer*	400 mg/m^2 IV over 120 min, loading dose, and 250 mg/m^2 IV over 60 min every 7 d, as maintenance	*Skin rash, infusion reaction,* asthenia, diarrhea, nausea
Bevacizumab *Colorectal cancer*	5 mg/kg IV over 60-90 min every 14 d	Asthenia, headache, epistaxis, proteinuria, GI perforations/ wound-healing complications, hypertension/hypertensive crisis

[a] FDA-approved uses in italics unless otherwise indicated; [b] Dose-limiting effects in italics

CLL = chronic lymphocytic leukemia; EGFR = epidermal growth factor receptor; NHL = non-Hodgkin's lymphoma

cell chronic lymphocytic leukemia.

In 2004, two new MAbs were approved by the US Food and Drug Administration (FDA) for the treatment of patients with advanced colorectal cancer: bevacizumab (Avastin) and cetuximab (Erbitux). Bevacizumab binds to the vascular endothelial growth factor (VEGF) and prevents ligand-induced VEGF receptor activation, which blocks the stimulation of endothelial cell growth and inhibits new blood vessel formation in tumors that secrete VEGF. Cetuximab binds the epidermal growth factor receptor (EGFR) on the surface of tumor cells, ultimately leading to downregulation of this signaling pathway. This process blocks tumor growth and proliferation and can reverse tumor resistance to chemotherapeutic agents such as irinotecan.

A recent randomized trial found that the addition of bevacizumab to irinotecan- and fluorouracil-based chemotherapy in newly diagnosed patients with

TABLE 7: Targeted therapies and their uses, dosages, and toxicities

Drug and its uses[a]	Dosages	Toxicities[b]
Imatinib *CML, GIST*	400 mg/d PO in chronic-phase CML and GIST; and 600 mg/day PO for CML in accelerated phase or blast crisis	Nausea and vomiting, edema and fluid retention, myalgias, diarrhea, myelosuppression, transaminitis
Gefitinib *NSCLC*	250 mg/d PO	*Acne-form skin rash, diarrhea*, transaminitis, asthenia, mild nausea and vomiting
Erlotinib *NSCLC*	150 mg/d PO	*Acne-form skin rash, diarrhea,* anorexia, fatigue, dyspnea
Bortezomib *Multiple myeloma*	1.3 mg/m^2 days 1, 4, 8, and 11 every 3 wk	*Diarrhea, peripheral neuropathy*, asthenia, fever, anorexia, nausea and vomiting, rash, headache, thrombocytopenia

[a] FDA-approved uses in italics unless otherwise indicated; [b] Dose-limiting effects in italics

CML = chronic myelogenous leukemia; GIST = gastrointestinal stromal tumor; NSCLC = non–small-cell lung cancer

SU011248 is an oral small molecule multitargeted tyrosine kinase inhibitor with antiproliferative and antiangiogenic activity attributed to the inhibition of PDGFR, VEGFR, KIT, and FLT3. In a recent phase II study of 63 patients with metastatic renal cell carcinoma, SU011248 resulted in a 33% partial response rate (95% confidence interval, 22% to 46%), a 37% rate of stable disease lasting at least 3 months, and a 1-year median survival of 65% (95% CI, 50% to 76%). Treatments were well tolerated, with major grade 3 or 4 toxicities consisting of lymphopenia, neutropenia, elevated amylase/lipase levels without associated pancreatitis, and fatigue or asthenia. If the results are confirmed, this study will have produced one of the highest response rates reported for single-agent therapy for patients with renal cell carcinoma (*Motzer RJ, Rini BI, Michaelson MD, et al: Proc Am Soc Clin Oncol 22:4500, 2004*).

advanced colorectal cancer significantly improved the response rate (45% vs 35%, $P = .0029$), duration of response (10.4 vs 7.1 months, $P = .0014$), and median survival (20.3 vs 15.6 months, $P = .0003$) compared with placebo. Grade 3 hypertension (10.9% vs 2.3%) and GI perforations (1.5% vs 0%) were more common in the bevacizumab arm, but overall, the bevacizumab therapy was thought to be well tolerated. This was the first randomized clinical trial demonstrating a survival benefit for antiangiogenic therapy.

Targeted therapies

Molecularly targeted therapies are designed to selectively interact with specific molecular pathways within cells to achieve a rational antitumor effect (Table 7). The classic rationally designed molecularly targeted agent is imatinib mesylate (Gleevec), which was identified in screening studies designed to detect inhibitors of the Bcr-Abl tyrosine kinase, present in virtually all cases of chronic myelogenous leukemia. Originally synthesized as an inhibitor of platelet-derived growth factor receptor, it is also a potent inhibitor of the

c-*kit* tyrosine kinase. Imatinib mesylate binds to the ATP binding site and inhibits the tyrosine kinase's ability to phosphorylate its substrates.

Gefitinib (Iressa) is another small-molecule–targeted therapy that is a signal transduction inhibitor of the EGFR tyrosine kinase. It binds noncovalently to the ATP binding site of the intracellular domain of the EGFR protein and blocks the kinase activity. Its anticancer effects arise from the ability to interfere with EGFR-mediated signaling, which is associated with cell proliferation, angiogenesis, and cell motility.

Erlotinib (Tarceva) is a HER1/EGFR-targeted therapy that has demonstrated a significant survival benefit as second-line therapy for patients with advanced NSCLC.

A randomized phase III study performed by the National Cancer Institute of Canada compared erlotinib (Tarceva) with best supportive care in patients with recurrent or refractory non–small-cell lung cancer following treatment with either one or two lines of prior chemotherapy. Erlotinib was significantly better than best supportive care in terms of response rate (8.9% vs < 1%, $P < .001$), disease progression-free survival (2.23 vs 1.84 months, $P < .001$), and median survival (6.7 vs 4.7 months, $P = .001$). Rash and diarrhea were the most frequent side effects, although only 5% of patients discontinued erlotinib due to drug-related toxicities. This is the first randomized trial of an EGFR inhibitor in lung cancer demonstrating a significant survival benefit (*Shepherd FA, et al: Proc Am Soc Clin Oncol 22:7022, 2004*).

Another targeted therapy is the 26S proteasome inhibitor bortezomib (Velcade). The 26S proteasome is a ubiquitous multiprotein complex responsible for degrading a variety of regulatory proteins involved in cancer cell proliferation. In multiple myeloma cells, bortezomib induces apoptosis by mechanisms that are not precisely defined. One hypothesis is that the inhibition of the proteasomal degradation of I-κB, an inhibitor of the transcription factor NF-κB, prevents the constitutive activation of NF-κB. In multiple myeloma cells, NF-κB is thought to be necessary for cell proliferation and survival.

The relevance of pharmacogenomics to molecularly targeted therapies was highlighted by the impressive finding that specific somatic mutations localizing to the ATP-binding site of the EGFR tyrosine kinase in lung tumors were associated with clinical response. In eight of nine patients with non–small-cell lung cancer (NSCLC) who responded to gefitinib therapy, specific mutations were identified, whereas none were found in seven matched nonresponders. This landmark finding, coupled with what is already known about c-kit mutations that "drive" the proliferation of gastrointestinal stromal cell tumors in response to imatinib therapy, suggests that it may ultimately be possible to prospectively select patients with NSCLC who have a high probability of responding to EGFR tyrosine kinase inhibitors. Further studies are under way to confirm these findings and to extend the observation to other tumor types.

See Appendix 3 for a list of drugs and/or new indications recently approved for treatment of cancer.

SUGGESTED READING

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